Effective Strategies for Population Studies of Acute Air Pollution Health Effects

by Morton Lippmann*

A series of field studies involving repetitive functional measurements in relatively small populations of healthy children and adults engaged in normal outdoor activities has shown that significant decrements in respiratory function are associated with exposures to ozone (O_3) at concentrations below the national ambient air quality standard. The ability to detect such effects can be attributed, at least in part, to the study design criteria used, which emphasized maximization of signal-to-noise ratios. Locations were selected to ensure relatively high exposures to relatively uniformly distributed secondary pollutants, with minimal exposure to local sources of primary pollutants. Populations were selected that would be engaged in active recreation out of doors. Populations of healthy persons were used to minimize variability in baseline function. We found that the magnitude of the O_3-associated decrements in respiratory function was dependent on the variability in sensitivity to O_3 among the population, the minute ventilation during outdoor activity, and the duration of the outdoor exposure. We also concluded that the O_3-associated responses were potentiated by the presence of other air pollutants.

Introduction

Studying natural populations for evidence of health effects associated with exposures to ambient air pollutants is a challenging task for a variety of reasons. Among the more difficult of these are: a) identifying an accessible population at risk whose relevant exposures can be defined and adequately characterized; b) specifying measurable indices of responses that may be expected to occur as a result of the exposures of interest; c) collecting an adequate amount of suitably quality-assured data on exposure and responses at times when exposures of magnitudes sufficient to elicit measurable responses actually occur; and d) collecting sufficient data on identifiable host characteristics and environmental exposures to other agents that may influence the response variables and confound any of the hypothesized pollutant exposure-response relationships that may be present. In addition, one must also account for the usual operational problems encountered in performing population studies, especially studies in the field, such as maintaining the motivation and skills of the field personnel for collecting reliable data; the cooperation of the subjects in producing reliable data; and access to sufficient numbers of subjects with the preselected characteristics in each category as may be needed.

Each of these design considerations has been stated in very general terms, and the specific problems encoun-

tered in trying to satisfy them could readily justify extended discussions. Such discussions are, however, probably not warranted here, or perhaps at all, since the generalities that can be stated will probably not help much in resolving any particular design problem that may arise. For example, we can state that we should know the roles of pollutant concentrations and exposure durations in eliciting the health responses of interest and the effects of other environmental factors in these responses before specifying the kinds of exposure data that are to be collected and/or analyzed. Unfortunately, these data will seldom, if ever, be available *a priori*. Rather than requiring such information in advance, which would greatly inhibit the initiation of some badly needed studies, we should collect sufficient data on exposure to permit correlation of responses with a variety of exposure indices.

This paper reviews the new approach to the design, performance, and analyses used by the NYU Institute of Environmental Medicine in a series of relatively small, highly focused field studies of acute functional responses in natural populations exposed to ambient air pollutants (1–4). The studies were conducted between 1980 and 1985 with the assistance and collaboration of colleagues at Harvard Medical School and the Health Effects Research Laboratory of the U.S. Environmental Protection Agency. The results from these studies, to be summarized in this paper, show that this kind of field study can be particularly productive. We have shown that measurable functional responses can occur among groups of healthy nonsmokers, both children and adults, engaged in normal activities at current ambient pollution levels.

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The observed responses were similar to, but generally greater in magnitude than those seen in studies elsewhere in which volunteers were exposed to ozone (O_3) in purified air for 1 or 2 hr while performing vigorous exercise.

Table 1 summarizes results from our most recent field studies of healthy adults and children along with those from a series of controlled exposures in chambers in other laboratories. In each of the chamber studies, vigorously excercising adults were exposed to O_3 for a defined period that was preceded and followed by exposure to purified air. Each study involved 60 min of exercise, either continuously, or with 15-min exercise periods interspersed with 15-min rest periods. It can be seen that the mean rate of functional change in the subgroup of our adults with minute ventilations closest to those in the chamber studies were higher than those for the group as a whole and also higher than those in the 1- and 2-hr exposures in chambers. The responses in the field study of normal, active children at summer camp, after adjustment for body size differences, were similar to those in our adult population and also greater than those in the chamber studies.

The greater responses observed in the field studies show that further laboratory studies are needed to establish the nature of the concentration-exposure time relationships for O_3 and the nature of the agents in the ambient mixture that can potentiate the characteristic O_3 response that occurs in controlled laboratory exposure tests at higher concentrations. Thus, the field studies have been useful not only for hypothesis testing, but also for hypothesis generation. As a result of our experience in these studies, we have established continuing lines of communication with colleagues at EPA's Clinical Studies

Laboratory in Chapel Hill, NC, to take advantage of the results of the controlled chamber studies in the design of field studies and to provide results from our field studies for their use in planning futher laboratory studies. In fact, our Fairview Lake summer camp study results, suggesting a cumulative daily O_3 exposure effect, led to a study at the EPA Clinical Studies Laboratory by Folinsbee et al. (5) involving 6¾ hr of exposure to O_3. This study conclusively established that functional decrements became progressively greater with duration of exposure. Since our study in adults involved exposures of less than 1 hr and had generally larger mean rates of functional change than the 1 and 2 hr chamber studies, we concluded that the effect of O_3 on lung function is potentiated by other environmental factors.

Strategic Design Considerations

The basic design premise in each of the field studies was to maximize the signal-to-noise ratio for the pollutant exposure versus response relationships. The noise on the response side of the relationships has been the focus of much work by others, and guidance on these aspects is available from the American Thoracic Society (ATS) (6,7). Accordingly, our focus was primarily on the reduction of the noise in the exposure variables.

Study Site Selection

The objective of our initial exploratory field study in 1980 was to determine whether the pollutants in the characteristic summer haze in the northeastern U.S. were producing any measurable acute health effects. The

Table 1. Mean functional changes per ppb O_3 after exercise: Comparison of results from field and chamber exposure studies with $O_3 \leq$ 180 ppb.

Study	No. of subjects and gender	Minute ventilation, L, mean ± SD	Exposure (exercise) time, min	O_3 concentration, ppb	Mean rate of functional change[a]			
					FVC, mL/ppb	FEV₁, mL/ppb	PEFR, mL/sec/ppb	FEF₂₅₋₇₅, mL/sec/ppb
Tuxedo adults (3)								
All 30	20M, 10F	78.6 ± 34.8	29.3 ± 9.2	21–124[b]	−1.9	−1.2	− 9.6	−3.9
44–70 L[c]	3M, 3F	57.5 ± 8.0	31.0 ± 7.9	21–124[b]	−3.5	−2.6	−12.6	−5.5
Gibbons and								
Adams (10)	10F	55	60 (60)[d]	150[e]	−1.1	−1.0	—	−0.6
Avol et al. (11)	42M, 8F	57	60 (60)	153[b]	−1.2	−1.3	—	—
				160[e]	−1.5	−1.5	—	—
McDonnell								
et al. (12)	22M	65	120 (60)	120[e]	−1.4	−1.3	—	−2.9
	20M	65	120 (60)	180[e]	−1.8	−1.6	—	−3.0
Kulle et al. (13)	20M	68	120 (60)	150[e]	−0.5	−0.2	—	−2.1
Linn et al. (14)	24M	68	120 (60)	160[e]	−0.7	−0.6	− 1.1	−1.1
Fairview Lake								
children (4)	53M, 38F	—	150–550	19–113[c]	−1.0	−1.4	− 6.8	−2.5
(adjusted to adult size)					(−2.1)	(−2.7)	(−14.0)	(−4.1)

[a]Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 sec; PEFR, peak expiratory flow rate; FEF₂₅₋₇₅, forced expiratory flow between 75 and 25% of vital capacity.
[b]Ozone concentration within ambient mixture.
[c]Minute ventilation, liters.
[d]Number in parentheses is exercise time when exercise is intermittent.
[e]Ozone concentration within purified air.

summer haze is regional in scale and enriched in secondary air pollutants such as O_3 and sulfuric acid (H_2SO_4), which form gradually during daylight hours in air masses containing diluted primary pollutants transported over long distances from industrial, power plant, and motor vehicle sources, i.e., sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and hydrocarbons (HC). We therefore sought a population in a community remote from local sources of air pollution, preferably in a wooded regional where ammonia (NH_3) sources, which would rapidly neutralize the H_2SO_4, would also be minimal. The community chosen for the 1980 study was Indiana, PA, a community previously studied by Speizer and colleagues as a control community for a study of the health effects of primary power plant plume effluents (8). Subsequent studies, which also focused on acute pulmonary function responses, were performed in wooded areas remote from the local pollution sources in New Jersey and New York (Fig. 1).

Population Selection

For the Indiana, PA, study in 1980, we selected a population of children attending a summer day camp program for three main reasons: a) cigarette smoking and occupa-
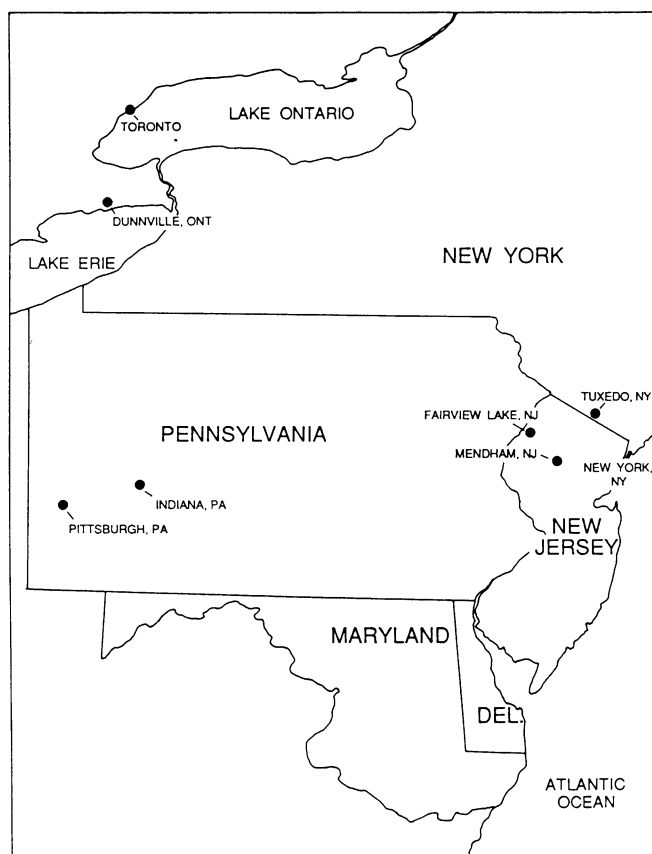

FIGURE 1. Locations of field studies of the health effects of exposure to summer haze air pollutants. Studies on respiratory function responses in children were conducted at summer camps in Indiana, PA, in 1980; in Mendham, NJ, in 1982; and Fairview Lake, NJ, in 1984. The study on adults exercising out of doors was conducted at Tuxedo, NY, in 1985.

tional exposure to lung irritants would not be confounding factors; b) the program of camp activities ensured that subjects would be out of doors and physically active during the daytime periods when O_3 and H_2SO_4 exposures would be highest; and c) the cooperation of the camp staff provided effective access to the children on a daily basis for the administration of functional tests and symptom questionnaires. Exposures to O_3 and H_2SO_4 are almost always higher outdoors than indoors, and, as regional scale secondary pollutants, their concentrations do not vary greatly from site to site within the camp's activity areas or from those measured at nearby samplers or monitors. In addition, there was little variation of activity level among the children in the camp program. Our 1982 and 1984 field studies used populations of children at summer camps in New Jersey and had the same advantages in terms of the absence of confounding exposure factors and a similarity in effective exposures to secondary air pollutants.

Our 1985 summer study on the effects of the summer haze pollutants on respiratory function in healthy non-smoking adults engaged in a regular program of outdoor exercise had a similar absence of confounding exposure factors, as well as similar exposures to the ambient secondary air pollutants. Each of the adult volunteers maintained a constant daily level and duration of exercise, but they differed widely from one to the other in these important variables. This increased the variability of the response among the population, but also provided a means of studying the influence of these variables on the responses.

Use of Sequential Measures of Response

For studies of acute responses to the inhalation of secondary air pollutants, which are distributed relatively uniformly over large geographic areas, it is not possible to identify a nonexposed or control population. On the other hand, the concentrations of the secondary pollutants have large temporal variations. There are both diurnal variations, with peak concentrations generally occurring in the afternoon, and day-to-day variations in concentration associated with the trajectory of the air mass over pollutant precursor source areas, atmospheric stability, intensity of incident solar radiation, temperature, and humidity. Thus, the volunteer subjects are exposed to different concentration profiles each day. By using repetitive measures of response, one can correlate variations in response with variations in exposure within the group.

For transient effects, data on day-to-day variability in response associated with day-to-day variability in exposure provides a sensitive tool for demonstrating the effects of pollutant exposures. The generally large intersubject variability in baseline values can be removed as a confounding factor because each subject's day-to-day variations can be considered individually. Another advantage is that the variability of responsiveness among individuals in a population can be directly assessed. Comparisons of individuals' degrees of pollutant-associated
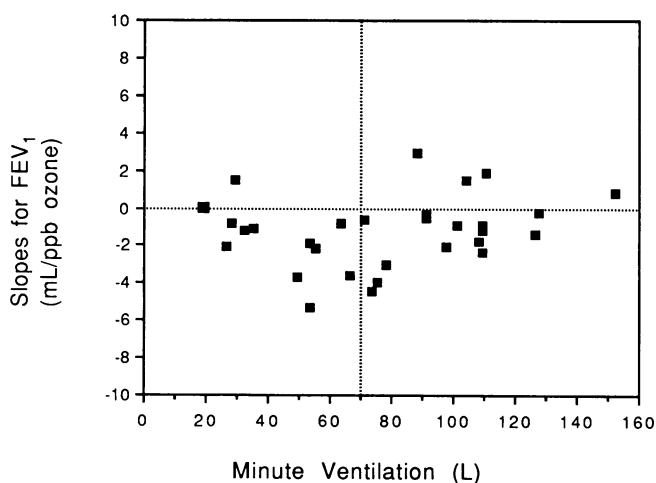
FIGURE 2. Plot of regression slopes for FEV_1 on concentration of O_3 for 30 adults engaged in daily outdoor exercise at Tuxedo, NY, in the summer of 1985 as a function of their minute ventilation during exercise.

responses, in relation to other characteristics of the individuals, may provide important clues as to the mechanisms that produce or influence responses. For example, Figure 2 shows results from our 1985 summer study in Tuxedo, NY, on the influence of minute ventilation on the rate at which ambient O_3 affects the forced expiratory volume in 1 sec (FEV_1) among adults engaging in outdoor exercise. The O_3-associated decrease in lung function with increasing minute ventilations up to 70 L was expected based upon compilations of data from studies of controlled exposures in chambers (9). None of the studies cited in the review had been done at minute ventilations above 70 L. The diminishing effect at the higher minute ventilations was unexpected. This provides a good example of how results from exploratory field studies can point the way to the need for more information on the role of basic physiological mechanisms.

Summary of Results of Acute Air Pollution Health Effects Studies

Our field studies of summer camp children and our study of healthy, nonsmoking adults engaging in a fixed daily regimen of outdoor exercise in the summer showed consistent responses to the pollutants in summer hazes. The O_3-associated decrements in spirometric functional indices in these studies were similar to, but greater in magnitude than, the decrements seen in controlled chamber studies involving 1 or 2 hr of exposure to O_3 in purified air and moderate to heavy levels of exercise during exposure. The effects in the field studies were almost as large as those reported in a chamber study involving 6¾ hr of exposure, which included 300 min of moderate exercise (5). There was a marked intersubject variability in the O_3-associated decrements in function, as has been reported in some of the chamber exposure studies.

All of the O_3 concentrations in our first and third camp

studies and nearly all in our adult exercise study were below the current primary National Ambient Air Quality Standard (NAAQS) for O_3 of 120 ppb for a 1-hr averaging time. These were the first studies to demonstrate O_3-associated respiratory function reductions for exposures below the NAAQS. Furthermore, in our study of 91 children in 1984, there were significant O_3-associated decrements in function for data subsets truncated above both 80 and 60 ppb O_3. This enabled us to conclude that there was no detectable threshold concentrations for the functional decrements.

While the functional decrements in the adults and children were quite similar, after appropriate adjustment for the differences in body size, their exposures were quite different. The children were continuously exposed to outdoor air while engaged in supervised recreational programs. The adults were indoors doing relatively sedentary tasks except for a single 15 to 55 min daily outdoor exercise period when their minute ventilation was markedly increased.

Since the adults' responses to less than 1 hr of exposure were greater than those seen in chamber studies with 1 to 2 hr of exposure at comparable exercise levels, it appears that other constituents in the ambient air potentiate the characteristic of O_3 response. Such a potentiation, along with their greater cumulative daily exposures, helps account for the greater responses in our children, in comparison with responses of children in chamber exposures (4), even though the camp children's exercise levels were lower than those of the children in the chamber studies.

In summary, the magnitude of the O_3-associated decrement in respiratory function depends on at least four critical factors: variations in sensitivity among a population of healthy persons; minute ventilation during exposure; duration of outdoor exposure; and the presence of other air pollutants.

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